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NEW ARYLPIPERAZINE DERIVATIVES USEFUL AS 5-HT_{1A} LIGANDS
[Nuevos derivados de arilpiperazinas utiles como ligandos 5-HT_{1A}]

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NEW ARYLPIPERAZINE DERIVATIVES /1*

The present invention concerns new compounds with general formula I, where X is $-(CH_2)_3-o-(CH_2)_4-$; m is equal to 0 or 1; n is equal to 1, 2, 3 or 4; Ar is 1-naphthyl, 7-benzofuranyl, 2,3-dihydro-1,4-benzodioxan-5-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl, phenyl or phenyl substituted by alkyl, halogen, trifluoromethyl, nitro, cyano, alkoxy, amino, alkylcarbamoyl, alkylsulfonamido or alkoxycarbonyl.

Various alternative methods for the preparation of these compounds are described, which present an affinity for the serotoninergic receptor $5\text{-}HT_{1A}$, which indicates its utility from the therapeutic point of view in the treatment of CNS disorders such as anxiety and depression.

ANTECEDENTS

Antecedents do exist on the important role played by the agonists of the $5\text{-}HT_{1A}$ receptor in the control of anxiety and depression (M. Hamon. 1994. *Trends Pharmacol. Sci.* **15:**36; P. Blier and C. Montigny, 1994. *Trends Pharmacol. Sci.* **15:**220). Up until now, the only commercialized $5\text{-}HT_{1A}$ agonist is buspirone. However, this drug lacks specificity for this receptor, since it can be bound to other types of receptors (dopinergic receptors, α_1 and α_2 adrenergic receptors, γ-aminobutyric acid (GABA)-

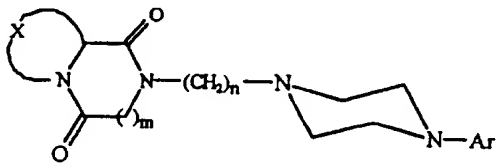
*Numbers in the margin indicate pagination in the foreign text.

benzodiazepin receptors and muscarinic acid receptors). On the other hand, their pharmacokinetic properties are not optimized and the duration of their activity is short (D. P. Taylor and S. L. Moon. 1991. *Neuropeptides* **19:**25; A. D. Levy and L. D. Van der Ker. 1992. *Life Sci.* **51:**83; K. V. Kastenholz and M. L. Crismon. 1984. *Clin. Pharm.* **3:**600). As a result, the search for more selective agents with better pharmacokinetic properties, and without the collateral effects of benzodiazepins, constitutes an important objective in the treatment of anxiety and depression.

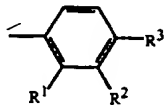
DESCRIPTION

The present invention concerns new arylpiperazine derivatives that have shown an elevated affinity for the 5-HT_{1A} receptor.

The new arylpiperazine derivatives are represented by general formula **I**:



I

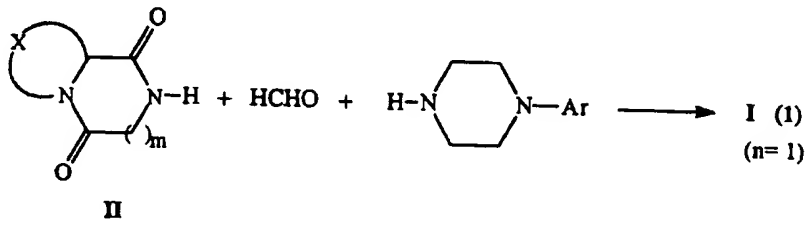
where X is $-(CH_2)_3-o-(CH_2)_4-$; ; m is equal to 0 or 1; n is equal to 1, 2, 3 or 4; Ar is  ,1-naphthyl, 7-benzofuranyl, 2,3-dihydro-1,4-benzodioxan-5-yl, 2,4-dihydro-2*H*-1,5-benzodioxepin-6-yl; in which R^1, R^2 and R^3 is hydrogen, alkyl, halogen,

/2

trifluoromethyl, nitro, cyano, alkoxy, amino, alkylcarbamoyl, alkylsulfonamido or alkoxycarbonyl.

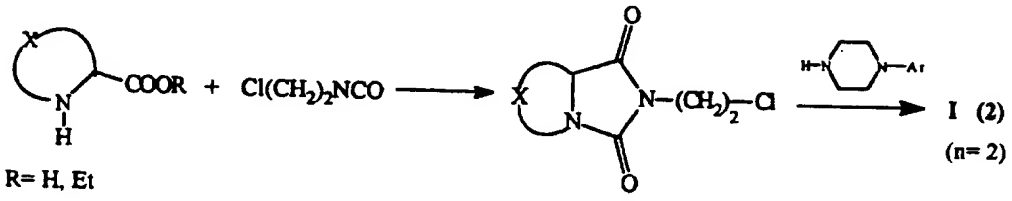
The compounds with general structural formula I were obtained by synthetic routes represented by the following diagram:

Method A



II

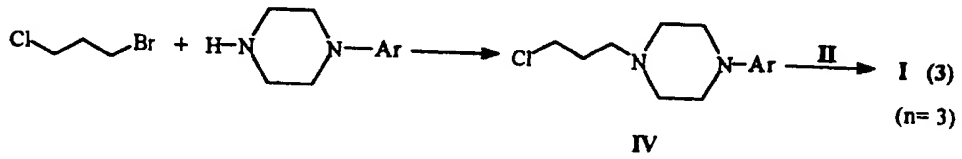
Method B



R= H, Et

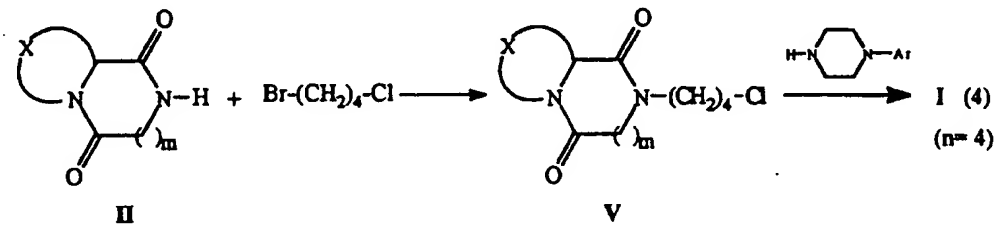
III

Method C



IV

Method D



II V

Products with formula **II** (X = $-(CH_2)_3-$, $-(CH_2)_4-$ and m = 0) /3 were synthesized by treatment of L-proline or D,L-pipecolinic acid with potassium cyanate and subsequent heating with hydrochloric acid according to those methods described by H. D. Dakin. 1920. *J. Biol. Chem.* **44:**499 and M. E. Freed and A. R. Day, 1960. *J. Org. Chem.* **25:**2108. The products with formula **II** (X = $-(CH_2)_3-$, $-(CH_2)_4-$ and m = 1) were prepared with the synthetic procedure described by T. Ueda et al. 1983. *Bull. Chem. Soc. Jpn.* **56:**568.

Those 1-arylpiperazines that have not been commercialized were obtained according to methods described in the literature: *J. Am. Chem. Soc.* **76:**1853 (1954); *J. Med. Chem.* **32:**1052 (1989); patent JP 61/152,655; *J. Med. Chem.* **31:**1934 (1988).

Compounds with general formula **I** (**1**)(n = 1) were obtained by the Mannich reaction of **II** with formaldehyde and 1-arylpiperazines (Method A).

Products with formula **III** were obtained by treating L-proline or ethyl pipecolinate with 2-chloroethyl isocyanate. The

substitution reaction of **III** with 1-arylpiperazines in the molar ratio of 1:1, by utilizing acetonitrile as a solvent in the presence of sodium carbonate, leads to compounds with general formula **I** (**2**)(n = 2)(Method B).

The compounds having formula **I** (**3**)(n = 3)(Method C) were synthesized by the reaction of **II** with 4-(3-chloropropyl)-1-arylpiperazine (**IV**), which were obtained from 1-bromo-3-chloropropane and the corresponding 1-arylpiperazine according to that method described by J. Bourdais. 1968. *Bull. Soc. Chim. Fr.*, 3246.

Compounds with formula **I** (**4**)(n = 4)(Method D) were synthesized by the treatment of **II** with 1-bromo-4-chlorobutane in the presence of sodium hydride in an atmosphere of nitrogen and subsequent treatment of the halogenated derivative **V** with the corresponding 1-arylpiperazine.

METHOD FOR THE REALIZATION OF THE INVENTION

EXAMPLE 1

Method A

2-(4-phenyl-1-piperazinylmethyl)-1,3-dioxoperhydroimidazole[1,5-α]pyridine, **1a**

1.57 g of phenylpiperazine were added to a suspension of 1,3-dioxoperhydroimidazole[1,5-α]pyridine (1.5 g) and 1 ml of formaldehyde at 35% in 20 ml of ethanol. The resulting

suspension is heated in a water bath for 1 hour. Once cooled, the reaction mixture is precipitated with 30 ml of water, yielding 3.1 g of **1a**, which is isolated in the form of dichlorohydrate. M. p. 178-180 °C.

The following compounds are prepared by analogous means:

2-[4-(*o*-methoxyphenyl)-1-piperazinylmethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.H_2O. M. p. 160-162 °C, **1b**

2-[4-(*m*-chlorophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.$3H_2O$. M. p. 176-178 °C, **1c** /4

2-[4-(*m*-trifluorophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 165-167 °C, **1d**

2-[4-(*p*-fluorophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.H_2O. M. p. 170-172 °C, **1e**

2-[4-(*m*-nitrophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.$1/2H_2O$. M. p. 176-178 °C, **1f**

2-(4-phenyl-1-piperazinylmethyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.$3/2H_2O$. M. p. 178-180 °C, **1g**

2-[4-(*o*-methoxyphenyl)-1-piperazinylmethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 168-170 °C, **1h**

2-[4-(*m*-chlorophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.$1/2H_2O$. M. p. 146-148 °C, **1i**

2-[4-(*m*-trifluoromethyl)-1-piperazinylmethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.H_2O. M. p. 158-159 °C, **1j**

2-[4-(*p*-fluorophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.H_2O. M. p. 180-182 °C, **1k**

2-[4-(*p*-nitrophenyl)-1-piperazinylmethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl.H_2O. M. p. 150-152 °C, **11**

2-[4-(*1*-naphthyl)-1-piperazinylmethyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.HCl.3/2H_2O. M. p. 256-259 °C, **1m**

EXAMPLE 2

Method B

2-(2-chloroethyl-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **IIIa**

4 ml of 2-chloroethyl isocyanate are added to a suspension of 5 g of L-proline in 50 ml of anhydrous acetone and heated for 2 hours in an atmosphere of nitrogen. The resulting solid is filtered and crystallizes in dioxane/chloroform, yielding 8.1 g of 1/(2-chloromethylcarbamoyl)-2-pyrrolidinecarboxylic acid, melting point: 154-156 °C. 30 ml of hydrochloric acid at 25% are added to 5 g of this acid, and the resulting solution is heated under reflux for 35 minutes. The solvent is eliminated under reduced pressure to obtain an oil that is dissolved in anhydrous acetone and dried over $MgSO_4$, 4.3 g of **IIIa** being isolated. E. p. 80-82 °C (0.01 mm of Hg).

2-(2-chloroethyl)-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine, **IIIb**

2.2 ml of 2-chloroethyl isocyanate are added drop by drop /5 to a suspension of 4 g of ethyl pipecolinate in 25 ml of anhydrous acetone and heated slightly for 2 hours in an

atmosphere of nitrogen. The solvent is eliminated under reduced pressure, 6.3 g of ethyl 2-(2-chloroethylcarbamoyl)pipecolinate being obtained. E. p. 150-152 °C (0.7 mm of Hg). A 10 % solution of potassium hydroxide in ethanol is added to 6 g of this ester until a basic pH is obtained. The resulting solution is heated in 25 ml of ethanol, under reflux, for 45 minutes. The solvent is eliminated under reduced pressure, the result being an oil that is dissolved in ethyl ether and dried over $MgSO_4$, 2 g of **IIIb** being isolated. E. p. 125 °C (0.4 mm).

2.27 g of 1-phenylpiperazine are added to a suspension of 3.25 g of **IIIb** and 2.93 g of sodium carbonate in 50 ml of acetonitrile. The resulting suspension is heated under reflux for 5 days. The reaction mixture is filtered while hot and the solvent eliminated under reduced pressure, an oil being obtained, which is chromatographed on a column of silica gel (ethyl acetate/ethanol 9:1), 2.52 g of an oil being isolated, which is transformed into the dichlorohydrate. The solid thus isolated is crystallized in chloroform/ethyl acetate. M. p. 193-195 °C.

Prepared in an analogous manner are the compounds:

2-[2-[4-(*o*-methoxyphenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.H_2O. M. p. 178-180 °C, **2b**

2-[2-[4-(*m*-chlorophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.HCl. M. p. 224-226 °C, **2c**

2-[2-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.HCl. M. p. 208-210 °C, **2d**

2-[2-[4-(*p*-fluorophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.HCl. M. p. 222-224 °C, **2e**

2-[2-[4-(*p*-nitrophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.HCl M. p. 252-254 °C, **2f**

2-[2-(phenyl-1-piperazinyl)ethyl]-1,3-dioxoperhydropyrrolo[1,2-*a*]imidazole. M. p. 116-118 °C, **2g**

2-[2-[4-(*o*-methoxyphenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 186-188 °C, **2h**

2-[2-[4-(*m*-chlorophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 174-176 °C, **2i**

2-[2-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 206-208 °C, **2j**

2-[2-[4-(*p*-fluorophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 296-198 °C, **2k**

2-[2-[4-(*p*-nitrophenyl)-1-piperazinyl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 130-132 °C, **2l**

EXAMPLE 3 /6

Method C

2-[3-(4-phenyl-1-piperazinyl)propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **3t**

2.2 ml of 1-bromo-3-chloropropane are added, in an inert atmosphere, to a suspension of 3 g of 1-phenylpiperazine and 3.07 g of anhydrous potassium carbonate in 18 ml of DMF. The resulting suspension is left at ambient temperature for 24 hours. The reaction mixture is filtered and the solvent eliminated under reduced pressure to obtain an oil that is chromatographed on a column of silica gel (ethyl acetate/hexane 1:1), 3.48 g of **IV**

(oil) being isolated.

0.52 g of sodium hydride at 60 % in mineral oil is added, in small portions, to a solution of 2 g of 1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine in 14.2 ml of anhydrous DMF. The reaction mixture is agitated for one hour at 60 °C. 3.48 g of **IV** in 14.2 ml of anhydrous DMF are added to this solution, drop by drop, and the mixture is heated to 110 °C for 2 hours. When the mixture has cooled, the solvent is eliminated under reduced pressure, the mixture is poured into water and extracted with CH_2Cl_2. The organic phase is dried over $MgSO_4$, the solvent eliminated under reduced pressure, and the resulting oil submitted to chromatography on a column of silica gel (methylene chloride/methanol 9.5:0.5), the result being 4.01 g of **3t**, which is isolated in the form of hydrochloride. M. p. 244-246 °C.

The following compounds are prepared in an analogous form:

2-[3-(4-phenyl-1-piperazinyl)propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.H_2O. M. p. 213-215 °C, **3a**

2-[3-[4-(*o*-methoxyphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazole[1,5-*a*]pyridine.2HCl.$3H_2O$. M. p. 208-210 °C, **3b**

2-[3-[4-(*m*-chlorophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 173-175 °C, **3c**

2-[3-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.$4H_2O$. M. p. 206-208 °C, **3d**

2-[3-[4-(*p*-fluorophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 205-207 °C, **3e**

2-[3-[4-(*p*-nitrophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 118-120 °C, **3f**

2-[3-[4-(*o*-tolyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 180-182 °C, **3g**

2-[3-[4-(*o*-propoxycarbonylphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.H_2O. M. p. 185-186 °C, **3h**

2-[3-[4-(*m*-ethylsulfoamidophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.$2H_2O$. M. p. 164-166 °C, **3i**

2-[3-(4-phenyl-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo [1,c-*c*]pyridine.2HCl. M. p. 210-212 °C, **3j** /7

2-[3-[4-(*o*-methoxyphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.H_2O. M. p. 212-214 °C, **3k**.

2-[3-[4-(*m*-chlorophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 164-166 °C, **3l**.

2-[3-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 150-152 °C, **3m**.

2-[3-[4-(*p*-fluorophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl. M. p. 230-232 °C, **3n**.

2-[3-[4-(*p*-nitrophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl. M. p. 244-246 °C, **3o**.

2-[3-[4-(*o*-propylcarbamoylphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 181-183 °C, **3p**.

2-[3-[4-(*m*-bromophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 205-207 °C, **3q**.

2-[3-[4-(*m*-aminophenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.$2H_2O$ M. p. 151-153 °C, **3r**.

2-[3-[4-(*o*-butoxyphenyl)-1-piperazinyl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 187-190 °C, **3s**.

2-[3-[4-(*o*-cyanophenyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.2HCl. M. p. 214-215 °C, **3u**.

2-[3-[4-(*o*-tolyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.2HCl. M. p. 259-261 °C, **3v**.

2-[3-[4-(*o*-propoxycarbonylphenyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.HCl.H_2O M. p. 69-70 °C, **3w**.

2-[3-[4-(*o*-methoxyphenyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.2HCl.H_2O M. p. 142-144 °C, **3x**.

2-[3-[4-(*o*-butoxyphenyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.2HCl.H_2O M. p. 187-188 °C, **3y**.

2-[3-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]propyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]imidazole.2HCl.H_2O M. p. 276-278 °C, **3z**.

EXAMPLE 4

Method D

2-[4-[4-(*o*-methoxyphenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **4t**

0.39 g of sodium hydride at 60% in mineral oil is added in /8
small portions, in an inert atmosphere, to a solution of 1.5 g 1,4-dioxohydropyrrolo[1,2-*a*]pyrazine in 10.1 ml of anhydrous DMF. The reaction mixture is agitated for 1 hour in 60 °C. 2.24 ml of 1-bromo-4-chloropropane in 4 ml of anhydrous DMF are added, drop by drop, to this solution, and the mixture is heated to 110 °C for 1.5 hours. When the mixture has cooled, the solvent is eliminated under reduced pressure, water is added to the residue and the mixture extracted with CH_2Cl_2. The organic phase is dried over $MgSO_4$ and the solvent eliminated under reduced pressure to obtain 2 g of **V** as a pale yellow oil. This oil is

dissolved together with 2.37 g of 1-(*o*-methoxyphenyl)piperazine in 16.5 ml of acetonitrile, 1.71 ml of triethylamine being added to the resulting mixture, which is heated under reflux for 18 hours. After the reaction mixture has cooled, the solvent is eliminated under reduced pressure and water added. The reaction mixture is extracted with CH_2Cl and the organic phase dried over $MgSO_4$. The solvent is eliminated under reduced pressure and the resulting oil chromatographed on a column of silica gel (methylene chloride/methanol 9.5:0.5), 1.44 g of **4t** being obtained, which is isolated in the form of dichlorohydrate. M. p. 204-206 °C.

Obtained in analogous form are the following compounds:

2-[4-(4-phenyl-1-piperazinyl)butyl]-1,3-dioxoperhydroimidazo[1,5-*a*] pyridine.2HCl.H_2O. M. p. 198-200 °C, **4a**

2-[4-[4-(*o*-methoxyphenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.H_2O. M. p. 199-201 °C, **4b**

2-[4-[4-(*m*-chlorophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 190-192 °C, **4c**

2-[4-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.1/2H_2O. M. p. 140-142 °C, **4d**

2-[4-[4-(*p*-fluorophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl.2H_2O M. p. 168-170 °C, **4e**

2-[4-[4-(*p*-nitrophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 200-202 °C, **4f**

2-[4-[4-(*m*-aminophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.3HCl. M. p. 167-169 °C, **4g**

2-[4-[4-(*o*-butoxyphenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.2HCl. M. p. 214-216 °C, **4h**

2-[4-[4-(*o*-propylcarbamoylphenyl)-1-piperazinyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine.HCl.3/2H_2O. M.p. 85-87 °C, **4i**

2-[4-(4-phenyl-1-piperazinyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 210-212 °C, **4j**

2-[4-[4-(*o*-methoxyphenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 178-180 °C, **4k**

2-[4-[4-(*m*-chlorophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 192-194 °C, **4l**

2-[4-[4-(*m*-trifluoromethyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*].2HCl. M. p. 176-178 °C. M.p. 176-178 °C, **4m** /9

2-[4-[4-(*p*-fluorophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.2H_2O. M. p. 194-196 °C, **4n**

2-[4-[4-(*p*-nitrophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl. M. p. 86-88 °C, **4o**

2-[4-[4-(*o*-cyanophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl. M. p. 185-186 °C, **4p**

2-[4-[4-(*m*-ethylsulfoamidophenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.2HCl.1/2H_2). M. p. 187-190 °C, **4q**

2-[4-[4-(*o*-tolyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl.3/2H_2O. M. p. 231-233 °C, **4r**

2-[4-[4-(*o*-propoxycarbonylphenyl)-1-piperazinyl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.HCl.3/2H_2O. M. p. 69-70 °C, **4s**

2-[4-[4-(*o*-butoxyphenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.2HCl.2H_2O. M. p. 188-190 °C, **4u**

2-[4-[4-(*m*-trifluoromethylphenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.HCl.H_2O. M. p. 182-183 °C, **4v**

2-[4-[4-(*o*-cyanophenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrido[1,2-a]pyrazine.HCl.H_2O. M. p. 98-100 °C, **4w**

2-[4-[4-(*o*-propoxycarbonylphenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrido[1,2-*a*]pyrazine.2HCl.$2H_2O$. M. p. 77-78 °C, **4x**

2[4-[4-(*o*-tolyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrido[1,2-*a*]pyrazine.HCl. M. p. 266-267 °C, **4y**

2[4-[4-(*m*-ethylsulfonamidophenyl)-1-piperazinyl]butyl]-1,4-dioxoperhydropyrido[1,2-*a*]pyrazine.2HCl. M. p. 219-220 °C, **4z**

EXAMPLE 5 /10

INHIBITION OF THE SPECIFIC BONDING OF ^{3}H-8-OH-DPAT TO THE SEROTONINERGIC RECAPTOR 5-HT_{1A} IN THE BRAIN OF THE RAT *IN VITRO*

The affinities of the some of those compounds with general structure **I** for the serotoninergic receptor 5-HT_{1A} in the membranes of the cerebral cortex of the rat was determined by means of radioligand techniques employing ^{3}H-8-OH-DPAT [8-hydroxy-2-propylamino)tetraline] as the selective ligand.

Procedure

Male albino rats (*Rattus norvegicus albinus*), Sprague-Dawley strain, with a weight of approximately 200 g are sacrificed by decapitation. The brains are rapidly extirpated and frozen in liquid nitrogen. The tissue is kept at -40 °C until the moment of its utilization.

The cerebral cortex is homogenized in 10 volumes of 50 mM Tris-HCl buffer, pH 7.7 at 25 °C, is centrifuged at 28,000 rpm for 15 minutes, at 4 °C. The supernatant is decanted and the sediment washed two times via resuspension and centrifugation under the conditions described. After a third washing, the resuspended sediment is incubated at 37 °C for 10 minutes. The membranes are centrifuged anew and resuspended in 10 volumes of Tris-HCl buffer with 5 mM $MgSO_4$ and 0.5 mM Na_2EDTA (pH 7.4 at 25 °C). 100 µl fractions of the final suspension of the membranes (5 mg/ml of protein) are incubated for 10 minutes at 37 °C with 0.6 nM ^3H-8-OH-DPAT in the presence or absence of the object compound of the study in a final volume of 1.1 ml of 50 mM Tris-HCl buffer. The nonspecific bonding is determined with 10 µM serotonin. The radioactive ligands are separated from the free ones by vacuum filtration on GF/B Whatman filters washed two times with 4 ml of 50 mM Tris-HCl buffer, pH 7.4 at 4 °C. After the filters have been dried for one hour at 60 °C, 4 ml of scintillation liquid (Aquasol) are added, and the reactivity bonded to the membranes measured by means of liquid scintillation spectrometry.

Six different concentrations of the drug are utilized for determination of the radioligand bond. The values obtained for the specific bond are represented directly as a function of the logarithm of the concentration of the inhibitor. The calculation

of the CI_{50} was carried out by means of nonlinear regression of the displacement curve, obtained by utilizing the equation $\%UE = 100(1 - C^b)/(CI_{50}{}^b + C^b)$. The conversion of the CI_{50} to K_j was carried out with the equation $K_j = CI_{50}/(1 + L/K_D)$, where L is the concentration of the radioligand and K_D its dissociation constant.

^{3}H-8-OH-DPAT from New England Nuclear. Specific activity approximately 141 Ci/mM.

The results obtained are presented in Table 1, together with the value of K_j for buspirone as a reference.

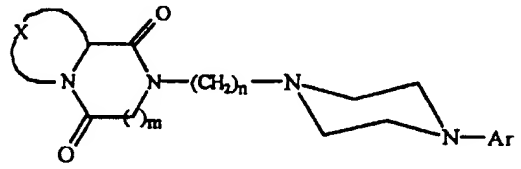
Table 1. Data on Affinity for the 5-HT_{1A} Receptor /11

Compound	Kj ± E.E. (nM)	Compound	Kj ± E.E. (nM)
1a	101 ± 8	3t	173 ± 44
1b	31.1 ± 1.7	3u	31.0 ± 5.9
1c	57.7 ± 5.7	3v	27.2 ± 1.7
1d	78.6 ± 7.5	3w	44.0 ± 3.1
1g	85.3 ± 3.1	3x	24.9 ± 11.1
1h	34.9 ± 0.7	3y	110 ± 15
1i	58.4 ± 1.1	3z	214 ± 21
1j	120 ± 10	4a	78.5 ± 6.8
1m	4.1 ± 1.1	4b	8.8 ± 0.9
2b	45.5 ± 4.6	4c	7.2 ± 0.6
2c	128 ± 10	4d	9.9 ± 0.9
2d	65.8 ± 3.1	4e	57.9 ± 3.2
2h	234 ± 20	4g	80.8 ± 18.1
2j	123 ± 11	4h	1.2 ± 0.1
3a	154 ± 10	4i	341 ± 106
3b	4.1 ± 0.6	4j	24.8 ± 1.4
3c	53.6 ± 1.5	4k	5.5 ± 0.7
3d	5.7 ± 0.7	4l	11.3 ± 1.0
3g	134 ± 2	4m	2.4 ± 0.6
3h	60.0 ± 5.6	4n	89.9 ± 5.2
3i	167 ± 29	4p	3.7 ± 0.8
3j	19.2 ± 1.5	4q	27.3 ± 5.9
3k	4.4 ± 0.6	4r	16.4 ± 2.3
3l	55.9 ± 9.1	4s	3.9 ± 1.4
3m	3.8 ± 0.5	buspirone	20.5 ± 2.3
3s	11.8 ± 2.9		

The terms in which this description has been drafted are /12
always to be taken with a broad and nonlimitative character.

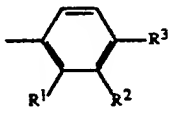
CLAIMS /13

1 - Compounds with general formula I:



I

in which:

X is $-(CH_2)_3-o-(CH_2)_4-$; ; m is equal to 0 or 1; n is equal to 1, 2, 3 or 4; Ar is  , 1-naphthyl, 7-benzofuranyl, 2,3-dihydro-1,4-benzodioxan-5-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl, where R^1, R^2 and R^3 are hydrogen, alkyl, halogen, trifluoromethyl, nitro, cyano, alkoxy, amino, alkylcarbamoyl, alkylsulfonamido or alkoxycarbonyl.

2 - A compound according to Claim 1, where X is $-(CH_2)_3-$, m is zero, n is 1 and Ar is a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, cyano, methoxy or amino.

3 - A compound according to Claim 1, where X is $-(CH_2)_4-$, m is zero, n is 1 and Ar is a phenyl optionally substituted by

methyl, fluoro, chloro, bromo, trifluoromethyl, cyano, methoxy or amino.

4 - A compound according to Claim 1, where X is $-(CH_2)_3-$, m is zero, n is 1 and Ar is 1-naphthyl.

5 - A compound according to Claim 1, where X is $-(CH_2)_3-$, m is zero, n is 2 and Ar is a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, cyano, methoxy or amino.

6 - A compound according to Claim 1, where X is $-(CH_2)_4-$, m is zero, n is 2 and Ar is a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, cyano, methoxy or amino.

7 - A compound according to Claim 1, where X is $-(CH_2)_3-$, m is 0 or 1, n is 3 and Ar is a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, cyano, methoxy, butoxy, amino, propylcarbamoyl, ethylsulfamido or propoxycarbonyl.

8 - A compound according to Claim 1, where X is $-(CH_2)_4-$, /14
m is 0 or 1, n is 3 and Ar is a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, cyano, methoxy, butoxy, amino, propylcarbamoyl, ethylsulfamido or propoxycarbonyl.

9 - A compound according to Claim 1, where X is $-(CH_2)_3-$, m is 0 or 1, n is 4 and Ar is 1-naphthyl, 7-benzofuranyl, 2,3-

dihydro-1,4-benzodioxan-5-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl or a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, cyano, methoxy, butoxy, amino, propylcarbamoyl, ethylsulfonamido or propoxycarbonyl.

9 - A compound according to Claim 1, where X is $-(CH_2)_4-$, m is 0 or 1, n is 4 and Ar is 1-naphthyl, 7-benzofuranyl, 2,3-dihydro-1,4-benzodioxan-5-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl or a phenyl optionally substituted by methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, cyano, methoxy, butoxy, amino, propylcarbamoyl, ethylsulfonamido or propoxycarbonyl.

10 - A procedure for obtaining compounds with general formula **I**, in which n is equal to 1, characterized by the reaction of **II** with formaldehyde and 1-arylpiperazines.

11 - A procedure for obtaining compounds with general formula **I**, in which n is equal to 2, characterized by the reaction of L-proline or of ethyl pipecolinate with 2-chloroethyl isocyanate and subsequent reaction for the substitution of the intermediate III with 1-arylpiperazines.

12 - A procedure for obtaining compounds with general formula **I**, in which n is equal to 3, characterized by the reaction of **II** with the corresponding 4-(3-chloropropyl)-1-arylpiperazines.

13 - A procedure for obtaining compounds with general formula **I**, in which n is equal to 4, characterized by the

reaction of **II** with 1-bromo-4-chlorobutane and subsequent treatment of the halogenated derivative with 1-arylpiperazines.

14 - Compounds with general formula **I** for utilization as medicines.

15 - Utilization of compounds with general formula **I** for the preparation of a medicine intended for the treatment of CNS disorders such as anxiety and depression.